MedicalXpress

Tumor PD-L2 expression may predict patient response to anti-PD-1 immunotherapy

June 15 2017

PD-L2 protein expression in human tumors was associated with clinical response to pembrolizumab (Keytruda), an anti-PD-1 immunotherapy, independent of PD-L1 expression, in patients with head and neck squamous cell carcinoma (HNSCC).

"It is well known that PD-1 has two binding partners, PD-L1 and PD-L2, yet most of the published work to date has looked at the distribution and predictive benefits of PD-L1 expression alone," said Jennifer H. Yearley, DVM, PhD, senior principal scientist of Anatomic Pathology at Merck Research Laboratories in Palo Alto, California. "We developed an assay that detects PD-L2 with a high degree of specificity and sensitivity to evaluate the prevalence of PD-L2 in human tumors and assess the relationship of PD-L2 expression with clinical response to pembrolizumab in patients with HNSCC."

How the Study Was Conducted and Results: First, Yearley and colleagues analyzed over 400 archival tumor samples across seven cancer types (renal cell carcinoma, bladder, melanoma, non-small cell lung cancer, triple negative breast cancer, gastric carcinoma, and HNSCC) with the novel immunohistochemistry assay. "We were very surprised to find how common PD-L2 expression was across all of the tumor types we evaluated," she said.

They also discovered that PD-L2 expression varied significantly among tumor types: gastric cancer and triple negative breast cancer showed generally moderate to high levels of expression, whereas expression in

renal cell carcinoma was predominantly low. Furthermore, over half of the HNSCC samples showed tumor cell expression of PD-L2, while tumor cell expression was not seen in any of the renal cell carcinoma and very few of the melanoma samples.

Next, Yearley and colleagues evaluated tumor samples from 172 patients with recurrent or metastatic HNSCC in two combined cohorts who had been assigned treatment with pembrolizumab during the KEYNOTE-012 trial. They found that clinical response was related to expression of PD-L2, suggesting that therapy targeting both PD-L1 and PD-L2 may enhance patient response.

"The overall response rate (ORR) for the two KEYNOTE-012 cohorts in this study was 27.5 percent among patients whose tumors were positive for both PD-L1 and PD-L2, more than two times higher than the 11.4 percent ORR for patients whose tumors were positive only for PD-L1," said Yearley. The researchers also found that PD-L2 positivity was associated with longer overall survival (OS), and median OS times were 303 days and 109 days respectively.

Author Comment: "We are all aware that PD-L1 is a marker with varying degrees of predictive ability in different tumor types," said Yearley. "There are individuals who are PD-L1 positive who don't respond, and people who are PD-L1 negative who do respond."

Overall, this study suggests that PD-L2 expression may provide additional information beyond PD-L1 positivity in predicting clinical response to anti-PD-1 therapies, Yearley noted.

As regards further ongoing work, expression of PD-L2 along with PD-L1 and other immune related analytes is included in a gene expression profile that reflects a T-cell inflamed tumor microenvironment, Yearley noted. This profile has been shown to be related to response to anti-PD-1

therapy and is currently being evaluated for potential diagnostic use in pembrolizumab clinical trials, she said.

Limitations: Limitations of the study include that the data obtained using the new assay was not compared with other standard detection and scoring methods, and a cutoff for PD-L2 expression levels associated with positive clinical response was not established, as this was an exploratory study.

The study was published in *Clinical Cancer Research* , a journal of the American Association for Cancer Research.

Provided by American Association for Cancer Research